

The Concept of Mild Cognitive Impairment in Personalized Medicine

Ingrid Rye^{a,b*}, Marek Kocinski^{a,c}, Alexandra Vik^a, Astri J. Lundervold^b, Alexander S. Lundervold^{a,d}

^aMohn Medical Imaging and Visualization Centre (MMIV), Department of Radiology, Haukeland University Hospital

^bDepartment of Biological and Medical Psychology, University of Bergen & K. G. Jebsen Centre for Research on Neuropsychiatric Disorders

^cDepartment of Biomedicine, University of Bergen & Mohn Medical Imaging and Visualization Centre, Department of Radiology, Haukeland University Hospital

^dDepartment of Computer science, Electrical engineering and Mathematical Science, Western Norway University of Applied Science

*Corresponding author: Ingrid Rye, Mohn Medical Imaging and Visualization Centre (MMIV), Haukeland University Hospital, Bergen, Norway. Tel.: +4795960783, ingrid.rye@hotmail.com

Introduction

Aging is characterized by cognitive changes, but phenotypic diversity makes it challenging to differentiate normal, age-related cognitive decline from aetiological decline caused by a neurodegenerative disease. This is true for Alzheimer's Disease (AD). The diagnosis is based on a pattern of impaired cognitive function, long after extensive neural degeneration has affected their brain. The intermediate state between normal cognitive aging and AD is referred to as Mild Cognitive Impairment. However, the group of MCI patients is very heterogeneous [1][2], and not all patients will show a trajectory towards dementia. For instance, it is empirically well-established that people with MCI have up to a ten-fold increased risk for developing AD [3, 4], but a substantial proportion also stabilizes at MCI and some may even revert back to normal cognition [5]. It is therefore of great importance to identify predictors of different trajectories among patients with MCI.

Method

Using data from the ADNI database, we will investigate differences in baseline scores on cognitive and global functioning between a group of adults with an MCI diagnosed maintained across all visits (sMCI, n = 285, age = 55-91 years) and adults progressing to AD at one time point during the examination period of minimum 3 collections (cAD), n = 335, range 55-88 years at inclusion. This poster represents a work in progress and in further analyses we attempt to identify and characterize clinical subtypes within this MCI population using a functional random forest (FRF) machine learning classification model as proposed by [6]. The model will be trained on measures of participants baseline scores on several measures for cognitive and global function, as well as neuropsychiatric symptoms. By using a functional FRF model we will be able to measure the proximity of each subject to every other subject, and as such generate a matrix for distance between participants. Further, we will use this matrix in a community detection algorithm to identify subgroups in the MCI sample.

Figure 1. Illustration of Random Forest.

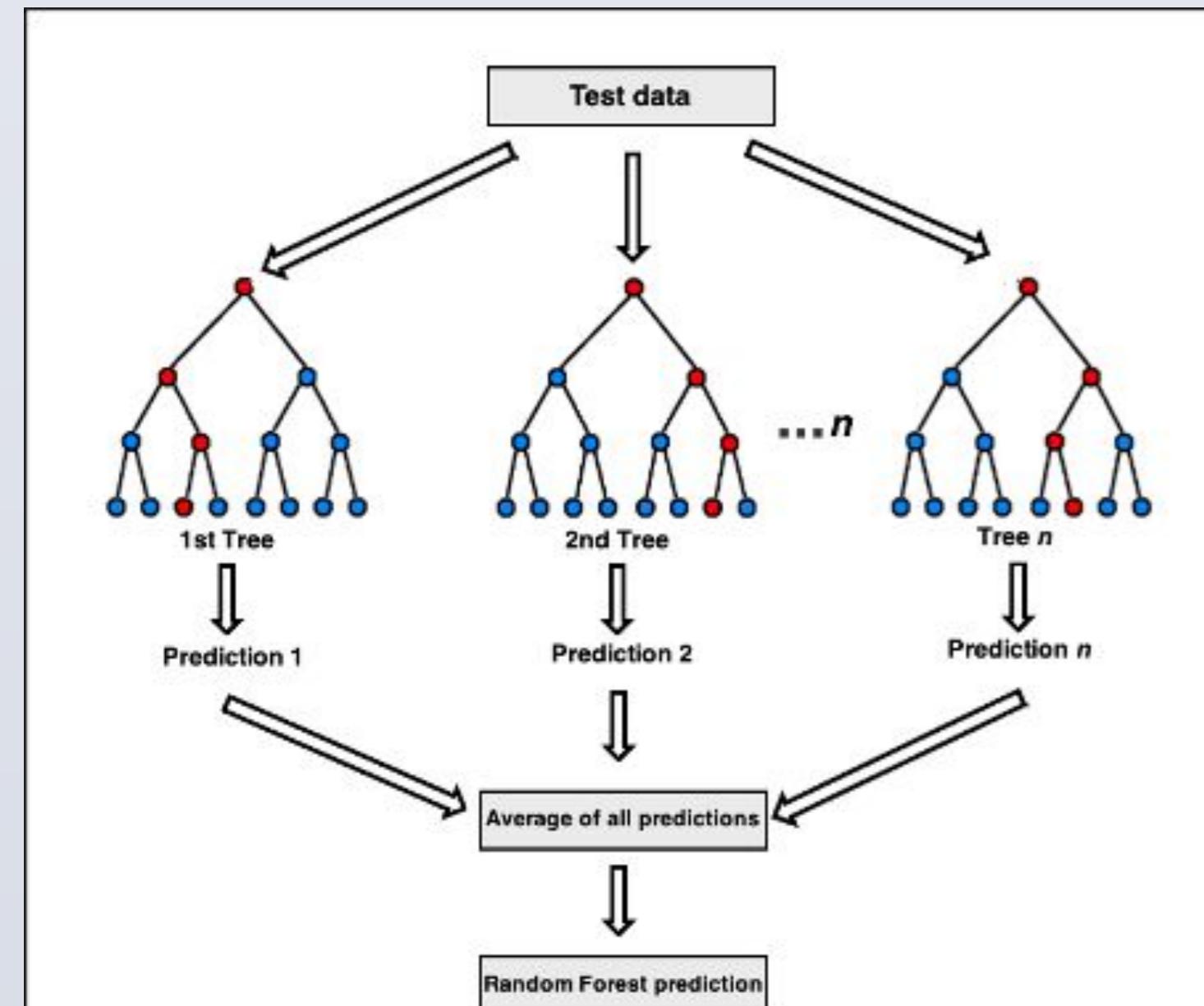
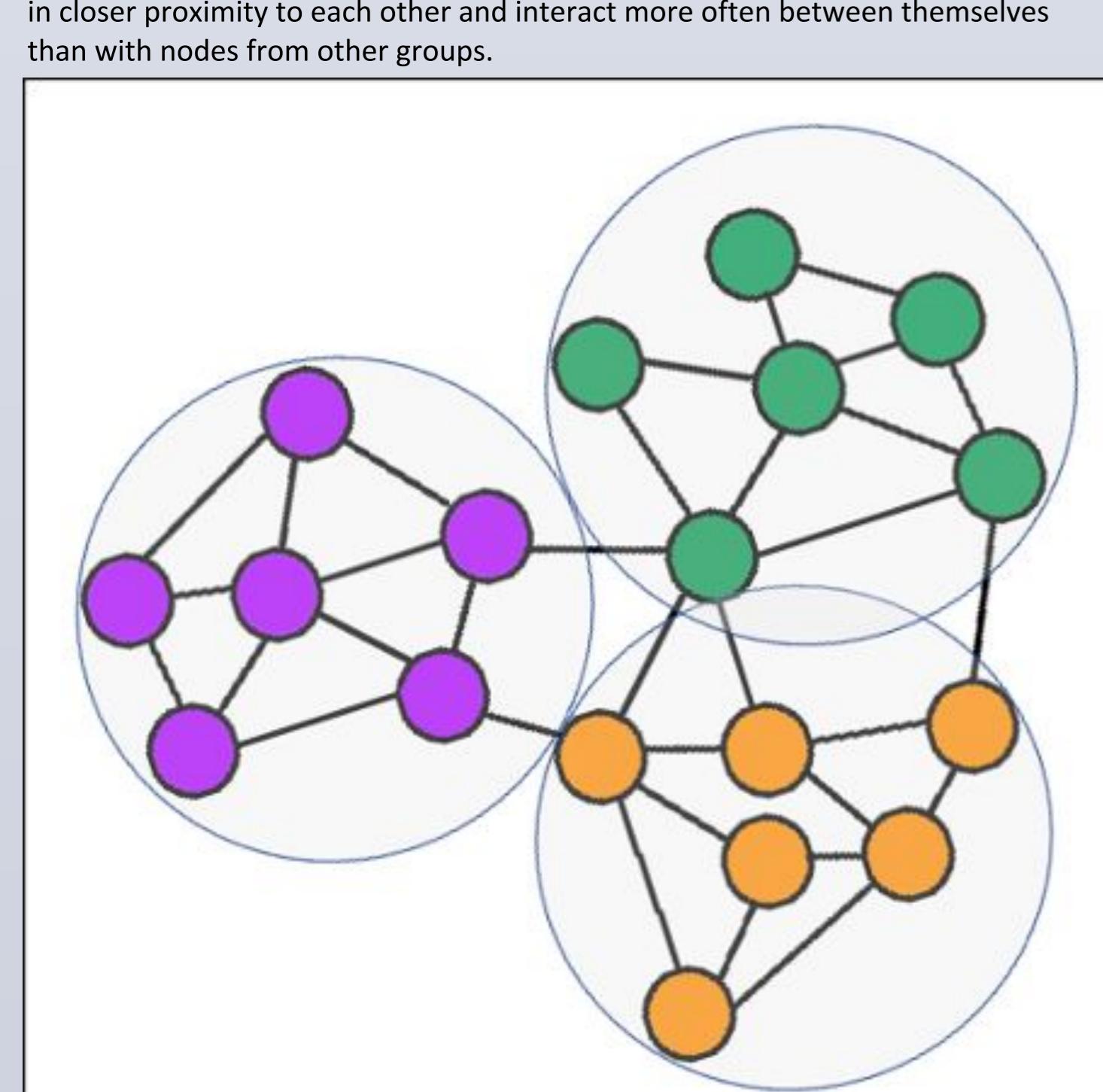


Figure 2. Illustration of a network represented by a node-link diagram with three communities detected. These network communities are groups of nodes that are in closer proximity to each other and interact more often between themselves than with nodes from other groups.



Preliminary results

Some preliminary exploration of data shows that the sMCI and cAD group had approximately equal gender distribution, and there was no significant difference in total age at baseline or total years of education between the groups. Further, the sMCI group scored significantly better on all selected tests of cognition and global function compared to the cAD group, and there were no significant differences in hippocampal volume across the groups (Table 1). Distribution for selected measures across the two groups and gender presented in figures below.

Table 1. Comparing demographics, hippocampal volume, cognition and global functioning at baseline between sMCI and cAD on.

	sMCI			cAD			<i>t</i>
	N	Mean	SD	N	Mean	SD	
Demographics							
Age, y	414	73.07	7.53	340	73.93	7.07	0.111
Education, y	414	15.93	2.90	340	15.90	2.76	0.182
Female, %	414	39.1		340	39.9		
Brain Volume							
Right Hippocampus	36	3468	562	26	3191	607	1.85
Left Hippocampus	36	3317	565	26	3120	634	1.29
Global function							
CDR	414	1.29	0.73	337	1.87	0.96	9.37***
ADAS 13	414	14.74	5.72	337	20.35	6.21	12.857***
Memory function							
RAVLT forgetting	414	4.39	2.50	340	5.10	2.22	4.047***
RAVLT immediate	414	36.69	10.49	340	29.36	7.81	10.678***
RAVLT learning	414	4.63	2.52	340	3.11	2.32	8.54***
Executive function							
Digit Symbol Substitution Test	134	38.25	10.88	206	35.83	10.93	0.046*
TMT: Part B	406	106.53	56.16	338	135.65	75.32	6.032***

Note: Digit Symbol Substitution Test discontinued after ADNI 1 protocol. Abbreviations: sMCI = stable mild cognitive impairment; cAD = converted Alzheimer's disease; CDR = Clinical Dementia Rating; ADAS = Alzheimer's Disease Assessment Scale; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail-Making Test. * *p* < .05. ** *p* < .01. *** *p* < .005.

Figure 3. Box and violin plots for right and left hippocampal volume for sMCI and cAD split by gender. Middle line illustrates the median and the whiskers display the range: 1.5*IQR (the full range of data). Outliers are plotted at separate dots.

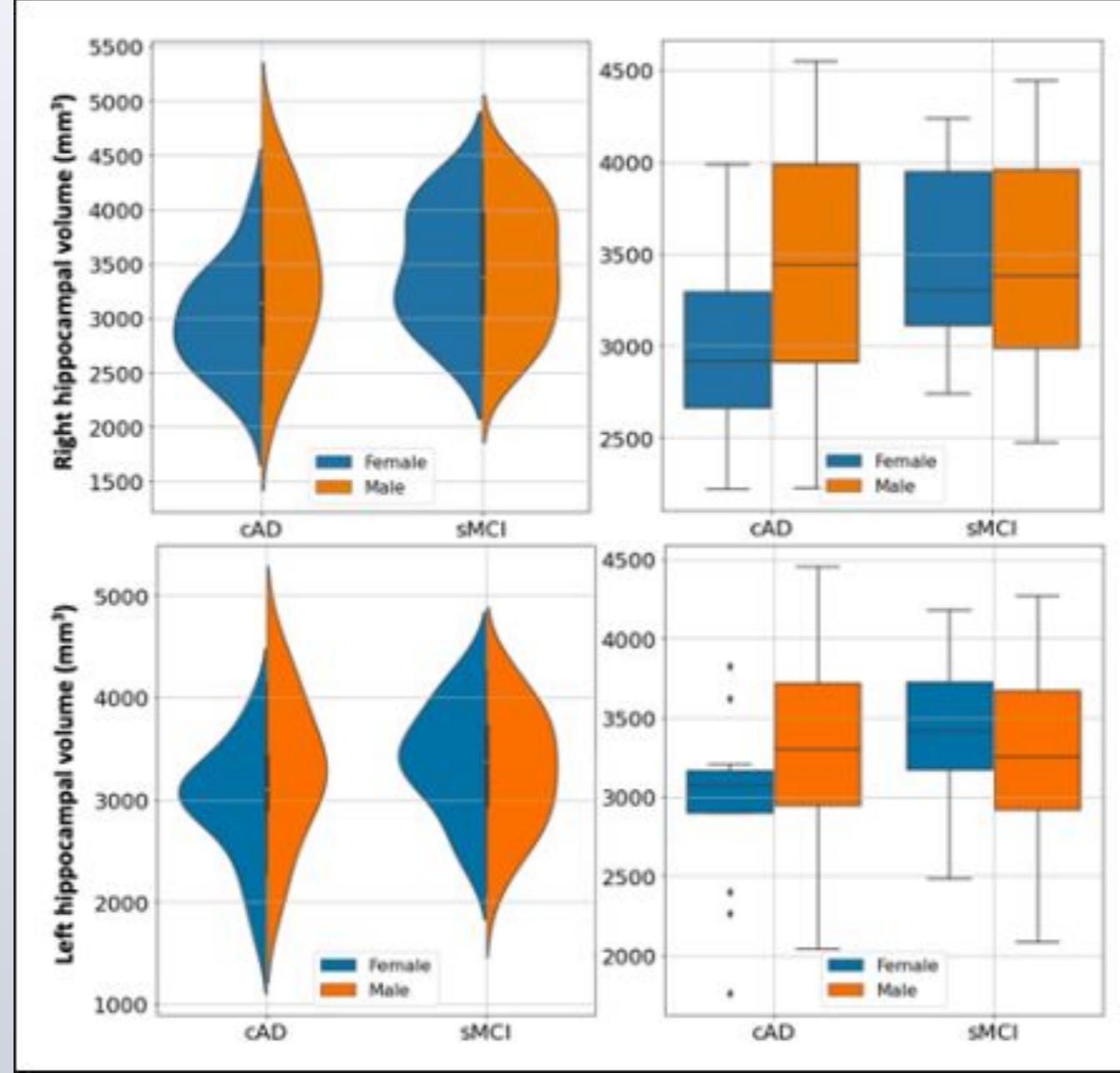


Figure 4. Box and violin plots for scores cognitive tests at baseline for sMCI and cAD split by gender. Middle line illustrates the median and the whiskers display the range: 1.5*IQR (the full range of data). Outliers are plotted at separate dots.

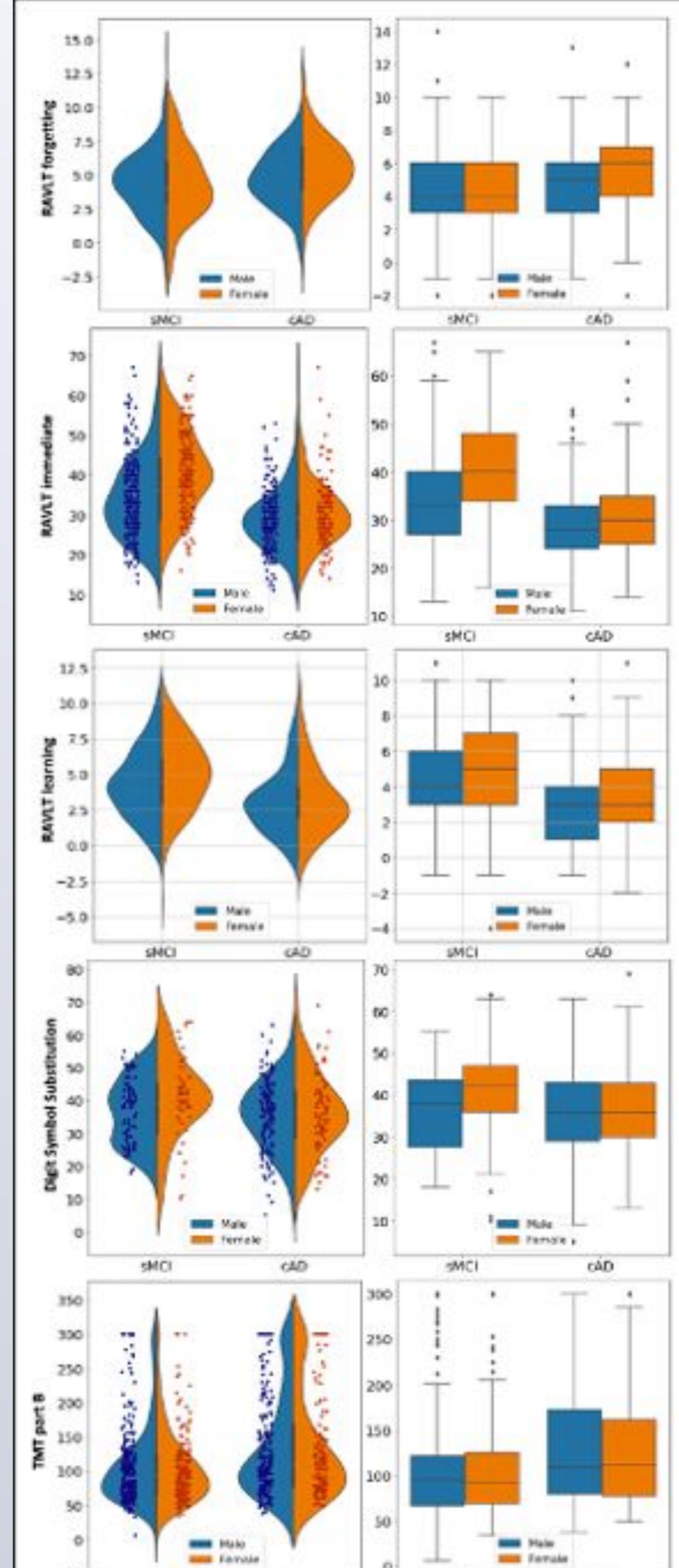
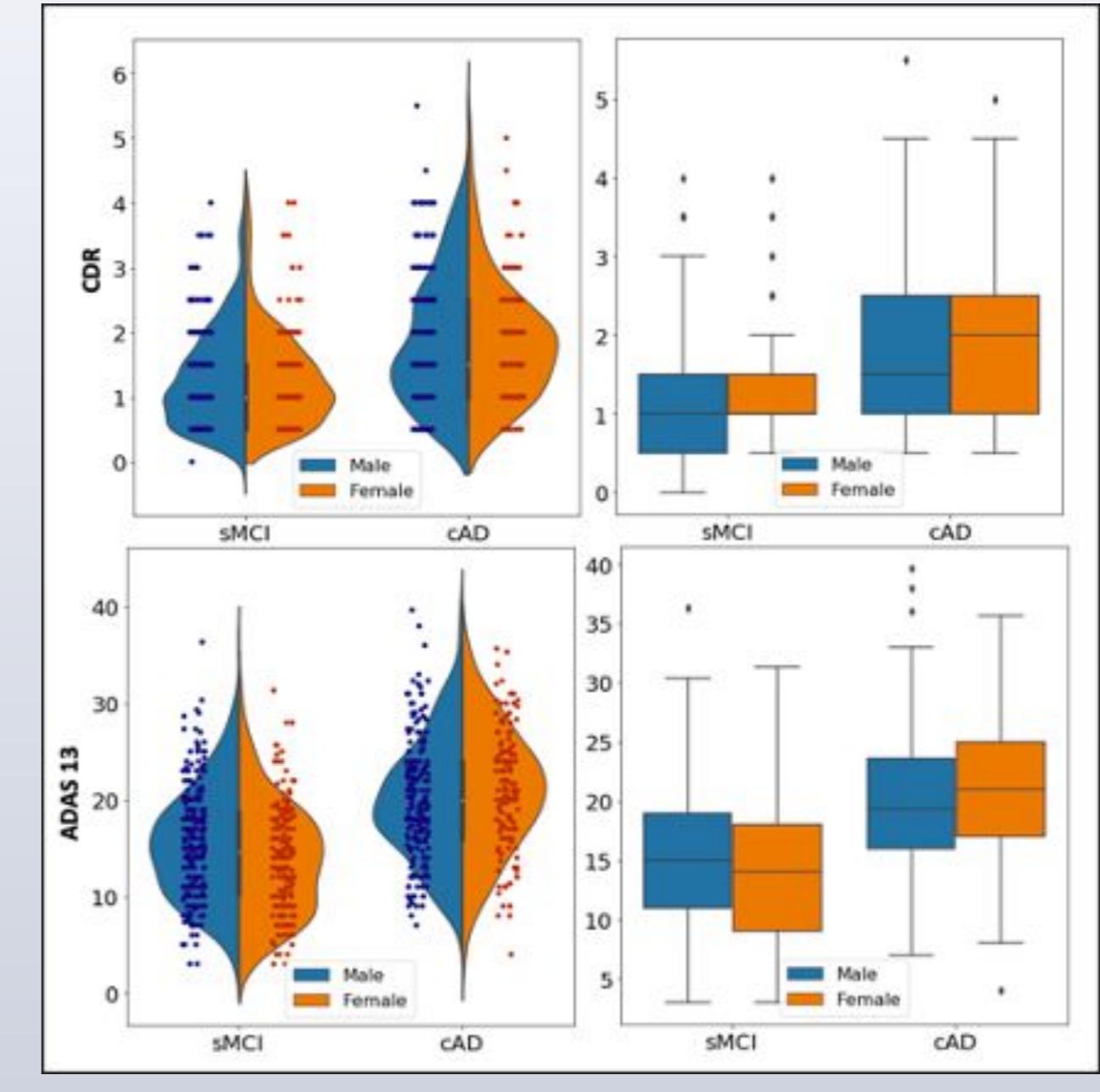


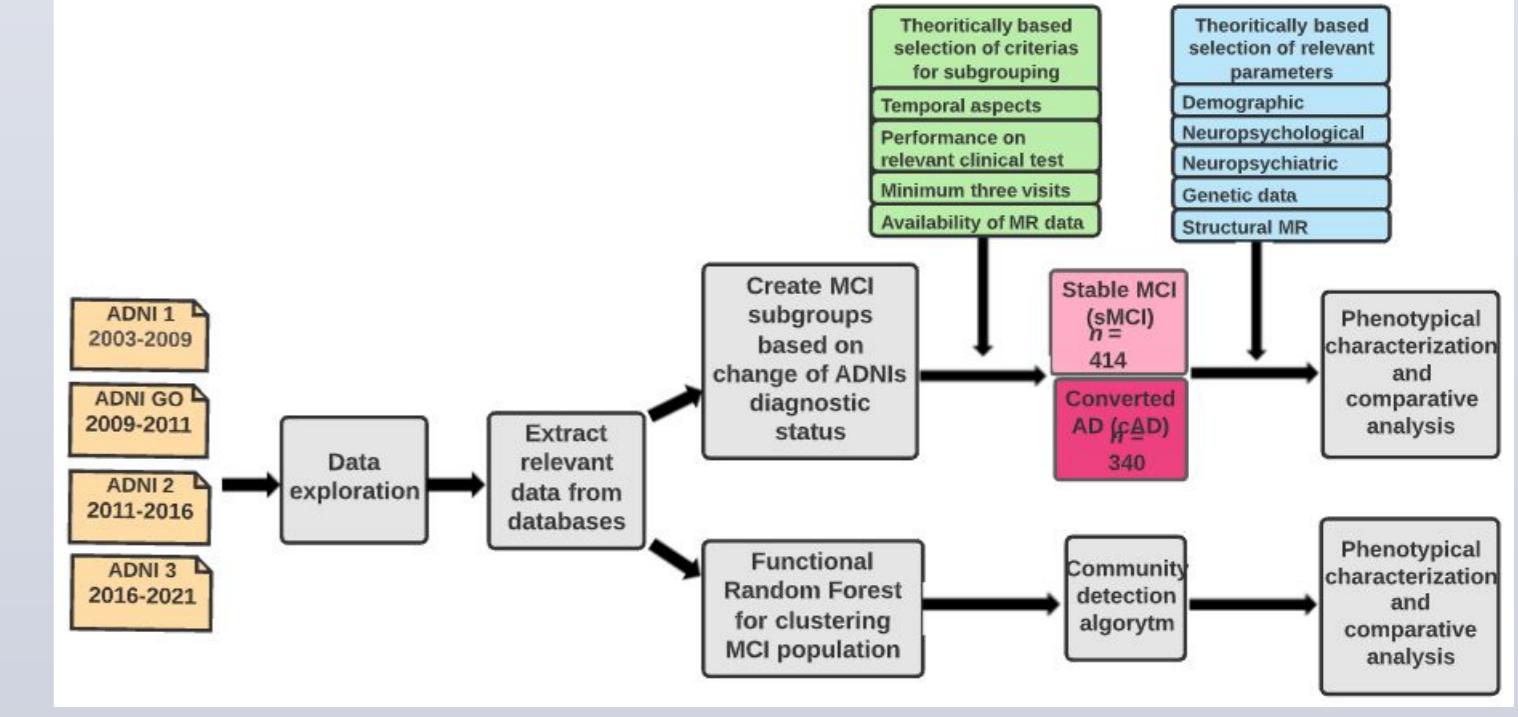
Figure 5. Box and violin plots for global function scores at baseline for sMCI and cAD split by gender. Middle line illustrates the median and the whiskers display the range: 1.5*IQR (the full range of data). Outliers are plotted at separate dots.



Discussion

Currently no curative treatment for AD exists and identifying individuals at risk for developing the disease at an early stage is therefore crucial. By using a RF machine learning model on clinical data we aim to identify meaningful clusters within the MCI cohort, and further find phenotypical characterizations of these subgroups which can be used to predict individual disease trajectories. This poster represents work in progress, and below is a flowchart representing the work process.

Figure 6. Flowchart showing work process.



Alzheimer's Disease Neuroimaging Initiative (ADNI)



ADNI is the result of efforts of many coinvestigators from a range of academic institutions and private corporations. It is a large and longitudinal natural history study initiated in 2003, still ongoing in its fourth study phase. The main motive of ADNI is to develop biological markers for early detection of AD pathology. In the ADNI project, biological, genetic, clinical and neuroimaging data (MRI and PET) have been collected yearly from several thousand participants with AD, MCI, as well as from a group of aged-matched controls with normal cognition. As modifications of the study protocols have been implemented across the four phases, some study data is available only for participants enrolled before/after certain protocols. Therefore, an important part is to get to know the large ADNI database. Further information about ADNI is available at adniinfo.org.

References

- [1.] Edmonds, E. C., Delano-Wood, L., Clark, L. R., Jak, A. J., Nation, D. A., McDonald, C. R., Libon, D. J., Au, R., Galasko, D. & Salmon, D. P. (2015). Susceptibility of the conventional criteria for mild cognitive impairment to false-positive diagnostic errors. *Alzheimer's & dementia: the Journal of the Alzheimer's Association*, 11(4), 415–424. <https://doi.org/10.1016/j.jalz.2014.03.005>
- [2.] Edmonds, E. C., Eppig, J., Bondi, M. W., Leyden, K. M., Goodwin, B., Delano-Wood, L. & McDonald, C. R. (2016). Heterogeneous cortical atrophy patterns in MCI not captured by conventional diagnostic criteria. *Neurology*, 87(20), 2108–2116. <https://doi.org/10.1212/WNL.0000000000003326>
- [3.] Petersen, R. C. (2000). Mild cognitive impairment or questionable dementia? *Archives of neurology* 57, 643–644.
- [4.] Boyle, P. A., Wilson, R. S., Aggarwal, N. T., Tang, Y. & Bennett, D. A. (2006). Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. *Neurology* 67, 441–445 (2006).
- [5.] Koepsell, T. D. & Monsell, S. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition: Risk factors and prognosis. *Neurology*, 79(15), 1591–1598. DOI: 10.1212/WNL.0b013e31826e26b7
- [6.] Feczkó, E., Balba, N.M., Miranda-Dominguez O., Cordova M., Karalunas, S.L., Irwin, L., et al (2017). Subtyping cognitive profiles in autism spectrum disorder using a functional random forest algorithm. *Neuroimage*, 172, 674–688. DOI: 10.1016/j.neuroimage.2017.12.044.